REMARKS

Status of the Claims

The Office Action of May 23, 2006 has been received and considered. Claims 1-32 were originally pending. Claims 4-13 and 19-32 have been canceled due to a restriction requirement. Claims 14-16 have now been canceled. Claims 1-3, and 17-18 remain pending. Claims 1, 17, and 18 have been amended. Reconsideration of the application in view of the amendment and following remarks is requested.

The Rejections of Claims 1-3 and 14-18 Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn:

Claims 1-3 and 14-18 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

Claims 1 and 14 were rejected by the Examiner as being vague and indefinite for recitation of "examining said collected material". The Examiner argues that there are no steps presented in the claims. The Applicants disagree that there are no steps in the claims; however, in order to more clearly set out the steps that were already specified in the claims, the Applicants have amended and reformatted claim 1 to call out the steps of the method of the present invention. Claim 14 has been canceled thus rendering the Examiner's argument moot.

The Examiner then questions how much sample is suppose to be filtered. The Applicants traverse the Examiner's contention that such information is necessary to satisfy the requirements of 35 U.S.C. §112, second paragraph. Claims should not rejected as unduly broad under 35

U.S.C. 112 for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art. *In re* Skrivan, 166 USPQ 85 (CCPA 1970). The amount of sample used in the method of the present invention would be within the level of ordinary skill in the art. Also, one of ordinary skill in the art would appreciate that the method of the present invention would work with many different types and amounts of biological samples. The Examiner has not pointed out why it is necessary to know the exact amount of sample in order to practice the method of the invention.

The Examiner then argues that in claim 14 is not clear what type of virus is being analyzed. Claim 14 has been canceled thus rendering the Examiner's argument moot. Further, the Examiner argues that simple filtration does not lend itself to the detection of "anything". The Applicants disagree. If the Examiner is arguing that the method of the present invention has no utility or that that the method is not enabling, then a rejected under 35 U.S.C. §112, second paragraph is improper. The simple subjective statement that a method which uses the principle of separating biological material through a filter is not good for the detection of "anything", without an explanation, is improper. More importantly, the Applicants are not claiming the use of a filter as a method of detection. The Applicants are claiming a method which separates cellular from non-cellular material and then subjecting the captured cells or cellular material to certain tests (as described in the specification) which determine whether or not the cells or cellular material contain the HPV virus. Thus, the method of the present invention uses filtration as a technique for separating material which is then subject to further analysis.

Lastly, the Examiner rejects claims 1 and 14 as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner argues that the omitted steps are steps to analyze and examine. The Applicants disagree. The Applicants are

puzzled as to the Examiner's statement that claims 1 and 14 lack the steps to analyze and examine the collected samples. Claim 1 recites:

> "...a method for analyzing a biological sample to detect cells infected by human papilloma virus (HPV), comprising: passing a medium containing said sample across a filter to collect material from said medium on said sample, said filter having a pore size that is greater than a dimension of a HPV particle but smaller than a dimension of a HPV infected cell; and examining said collected material to determine if HPV infected cells are present in said material." (emphasis added)

If the Examiner is arguing that the claims lack a step of examining, then this analysis is clearly mistaken. If the Examiner is arguing that specific examples of analysis or examination of collected material are needed as further limitations of the claims as essential steps, then the Applicants disagree. The Applicants should not be limited to certain technologies or methodologies for the detection of infected cells when such technologies would clearly be known to one or ordinary skill in the art. Such analysis or examination steps are not essential nor has the Examiner demonstrated why such steps would render the claims incomplete.

Accordingly, for the reasons stated above, the rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejections of Claims 1-3 and 14-18 Under 35 U.S.C. §112, First Paragraph Should be Withdrawn:

Claims 1-3 and 14-18 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner argues that the Applicant's disclosure is deficient. The Applicants respectfully disagrees.

The Examiner argues that the entire teaching of the Applicant's specification is directed to simple filtration of cells that are supposedly infected with virus. The Applicants disagree. The present invention teaches a method for analyzing a biological sample to detect the presence or absence of cells infected by HPV by obtaining a sample from a patient, placing the sample in a liquid medium; passing the medium containing the sample across a filter to collect cells from the medium on the filter, and examining the collected cells to determine if HPV infected cells are present. The Examiner asks the question "[h]ow does utilization of cell filtration relate to detection or analysis of infected cells?" The simple answer to the Examiner's question is that filtration is the technique used to process a biological sample before it is analyzed for the presence or absence of infected cells. The Examiner argues that none of the shortcomings that the Applicants have specified in their application have been addressed. The Applicants disagree. In the background section of the Applicant's specification is a description of one of the shortcomings in the current state of the art:

> "Therefore, in a diagnostic procedure, it would be desirable to prepare a sample such that it contains no or a fewer number of extracellular HPV, and to base a diagnostic result on such prepared sample. Thus, the determination of HPV cells will correlate more closely with a diagnosis of LGSIL than with a diagnosis of "Within Normal Limits" (WNL)." (emphasis added)

Thus, the filter system of the Applicant's invention allows a practitioner to answer the question of whether or not a sample taken from a patient contains cells infected with a virus. If cells are not infected, then extracellular viral particles would be washed through the filter leaving uninfected cells. For example, a sample currently taken from a patient (e.g., cervical swab) when tested for HPV (e.g., Digene HPV Test) can only determine if HPV is present in the sample.

What cannot be tested is whether or not the HPV found in the sample is from extracellular HPV or intracellular HPV (or both). The reason that this is so important has been explained previously, i.e. that the presence of extracellular HPV in a biological sample leads to a completely different diagnosis than the presence of intracellular HPV in a sample. The method of the present invention provides a tool which can facilitate such a decision. Thus, the same sample mentioned previously can be suspended in medium, passed over a filter which has a pore size that is greater than a dimension of a HPV particle but smaller than a dimension of a HPV infected cell, and the collected cells analyzed for the presence of HPV (meaning intracellular HPV since extracellular HPV would pass through the filter). The Applicants have provided examples by which one of ordinary skilled in the art may examine the collected cells or cellular material. For instance, on page 5, lines 1-4, of the specification, the Applicants have described two such methods:

> "...the materials collected on the filter may be prepared and examined by placing the collected material onto a slide for viewing under a microscope, or by using a Hybrid Capture™ method as described herein."

Thus, the Applicants have taught a method of analyzing a biological sample to detect the presence or absence of cells infected by HPV by obtaining a sample from a patient, placing the sample in a liquid medium; passing the medium containing the sample across a filter to collect cells from the medium on the filter, and examining the collected cells to determine if HPV infected cells are present.

In light of the preceding explanation and examples, the Examiner's subsequent questions as to how many cells, requirements for culturing cells, etc. can be seen to be irrelevant to the proper application of the method of the present invention.

The Applicant has provided sufficient guidance with respect to a method for analyzing a biological sample to detect cells infected by a virus. One skilled in the art would be able to routinely filter biological specimens through a filter which retains cells but allows for extracellular viruses to pass through and then test those remaining cells to see if any are infected. All of these steps outlined by the Applicant can be completed without undue experimentation.

Accordingly, for all of the reasons stated above, the rejections under 35 U.S.C. § 112, first paragraph should be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

In the Office Action, claims 1-3 and 14-18 were rejected under 35 USC §103(a) as being unpatentable with respect to U.S. Patent No. 5,942,700 to Radcliffe *et al.*

In the Office Action, it is asserted that the patent to Radcliffe *et al.* discloses a method of collecting samples including biological samples through a filter. The Examiner also states that "...one of ordinary skill in the art at the time of filing would have been highly motivated by the teaching of Radcliffe *et al.* to use the method for collecting of infected cells, including cells infected with papillomavirus." (see page 6 of the Office Action). The Applicants respectfully disagree.

The Court of Appeals for the Federal Circuit has forcefully stated that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

> "[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

> In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to

> combine them to render the claimed invention obvious."); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).
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> ... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

The motivation cited in the present Office Action for the proposed combination is as follows:

> "...one of ordinary skill in the art at the time of filing would have been highly motivated by the teaching of Radcliffe et al. to use the method for collecting of infected cells, including cells infected with papillomavirus. The cited patent taught collection of biological sample which broadly incorporates cells, including infected cells." (see page 6 of the Office Action).

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak*. The claims here are no more obvious than those at issue in *Dembiczak*. There is no clear, particular suggestion or motivation in the prior art to make the specific combination of "a method for analyzing a biological sample to detect the presence or absence of cells infected by HPV by obtaining a sample from a patient, placing the sample in a liquid medium; passing the medium containing the sample across a filter to collect cells from the medium on the filter, and examining the collected cells to determine if HPV infected cells are present", much less for the claims dependent thereon with their additional limitations. The patent to Radcliffe *et al.* does not contemplate a method for the separation of viral particles from cells. Radcliffe *et al.* never teaches or discloses how to make, or how to use, or how to test for the presence or absence of cells infected with a virus – in fact, Radcliffe *et al.* never teaches or discloses that a skilled artisan would ever need or want to make such a determination. The argument by the Examiner that because Radcliffe *et al.* mentions the filtering of biological materials it necessarily would include the filtering of infected cells is clearly improper. *Prima facie* obviousness has not been established under such conditions. There is no clear, particular motivation in Radcliffe *et al.* to reach the claimed invention. Withdrawal of this rejection under 35 USC 103(a) is respectfully requested.

The Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

In the Office Action, claims 1-3 and 14-18 were rejected under 35 USC §102(e) as being anticipated by or, in the alternative, under 35 USC §103(a) as obvious with respect to U.S. Patent No. 6,905,594 to Ferguson.

In the Office Action, it is asserted that the patent to Ferguson discloses a method of capturing materials suspended in a liquid utilizing a filter apparatus. The Examiner also states that Ferguson does not teach a pore size for the filter however the pore size is "...a design choice unless the proof is critically proven." (see page 6 of the Office Action). The Applicants respectfully disagree.

The patent to Ferguson does not contemplate a method for the separation of viral particles from cells. Nowhere in Ferguson can the Examiner point to such a statement or teaching. The Examiner states that the pore size is a design choice, however, such a pore size is critical for the method step to work properly. A filter that has too large a pore size will allow cells to pass through the filter. A filter with to small a pore size would prevent viral particles from passing through the filter and thus a practitioner would not be able to differentiate between viral particles which have infected cells and those particles which are extracellular. Ferguson never teaches or discloses how to make, or how to use, or how to test for the presence or absence of cells infected with a virus – in fact, Ferguson never teaches or discloses that a skilled artisan would ever need or want to make such a determination.

Therefore, contrary to the position taken in the Office Action, the Patent to Ferguson does not teach all the limitations of the claims of the present invention. Withdrawal of the rejection is requested.

CONCLUSION

For all of the above-discussed reasons, Applicant respectfully submits that claims 1-3, and 17-18 are allowable and that the application is now in condition for allowance. A notice to

this effect is earnestly solicited. It is believed that no fee is required for this submission. If any fees are required or if an overpayment is made, the Commissioner is authorized to debit or credit our Deposit Account No. 502855, accordingly. If any questions or issues remain, the resolution of which the Examiner feels would be advanced by a conference with Applicant, the Examiner is invited to contact Applicant's attorney at the number noted below.

Respectfully submitted,

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